Induced Hypotension During Anesthesia, with Special Reference to Orthognathic Surgery

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Since Gardner first used arteriotomy during anesthesia to improve visibility in the surgical field, various techniques and pharmacological agents have been tried for the same purpose. With reports documenting the spread of acquired immune deficiency syndrome through blood transfusions, prevention of homologous blood transfusions during surgery has also become a major concern. Induced hypotension has been used to reduce blood loss and thereby address both issues. In orthognathic surgery, induced hypotension during anesthesia has been used for similar reasons. It is recommended that hypotensive anesthesia be adjusted in relation to the patient's preoperative blood pressure rather than to a specific target pressure and be limited to that level necessary to reduce bleeding in the surgical field and in duration to that part of the surgical procedure deemed to benefit by it. A mean arterial blood pressure (MAP) 30% below a patient's usual MAP, with a minimum MAP of 50 mm Hg in ASA Class I patients and a MAP not less than 80 mm Hg in the elderly, is suggested to be clinically acceptable. Various pharmacological agents have been used for induced hypotension during orthognathic surgery. In addition, there are many drugs that have been used in other types of surgery that could be used in orthognathic surgery to induce hypotension. Recent reports using control groups do not show significant differences in morbidity and mortality attributable to induced hypotension during anesthesia. Appropriate patient evaluation and selection, proper positioning and monitoring, and adequate fluid therapy are stressed as important considerations in patients undergoing induced hypotension during orthognathic surgery.

Orthognathic surgery involves the surgical correction of oral and facial deformities involving bones and soft tissues. There is significant bleeding from both incised soft tissues and bones during these procedures due to the rich blood supply to the areas involved. Considerable bleeding from the bone occurs because most of the vessels traversing the bones cannot be identified and isolated before or after osseous sectioning. In addition, severe bleeding may occur during maxillary osteotomies from damage to the descending palatine artery, sphenopalatine artery, pterygoid venous plexus, or occasionally from damage to the second part of the maxillary artery. Severe bleeding can also occur during mandibular osteotomies from damage to the masseteric artery, retromandibular vein, pterygoid venous plexus, or occasionally from damage to the facial artery. Furthermore, due to limited access, poor visibility to isolate and ligate or cauterize vessels that otherwise would have been ligated or cauterized with ease adds to the problem of bleeding during orthognathic surgery, frequently obscuring the operative field.

In order to help the surgeon reduce bleeding and to improve visibility in the operative field, many anesthetists have employed induced hypotension during orthognathic surgery. Induced (or controlled) hypotension is a method by which the arterial pressure is decreased in a predictable and deliberate manner. Unlike in procedures such as aortic surgery, where hypotensive anesthesia is often employed and where the bleeding vessel can often be identified, in orthognathic surgery bleeding vessels may not be identified. Although it is similar to lumbar surgery in this respect, orthognathic surgery differs from the latter in that large areas of medullary bone are exposed during orthognathic surgery, which contributes to the blood loss. Patients who undergo aortic and lumbar surgery are often old and medically compromised, whereas patients who receive orthognathic surgery are usually young and healthy. Thus, the risks of hypotensive anesthesia in orthognathic surgery are far less than in aortic or lumbar surgery.

Several controlled[1-4] and uncontrolled studies[5] have demonstrated that induced hypotension improves the quality of the surgical field in orthognathic surgery. One study, by Fromme et al,[6] disputes this finding. In this study, though the assessment was by surgeons who were

blind to the method of anesthesia, the comparison was of operations on both maxillas and mandibles. The specific operations were not stated. The degree of blood loss during different maxillary and mandibular osteotomies may differ. Furthermore, the frequency or the time of assessment, which may influence the outcome, was not stated. In a study conducted on patients undergoing specific operations of the maxilla and mandible, where assessments were carried out at frequent intervals by a similar blind method, there was a significant improvement of the quality of the surgical field.[4] A newer technique of estimation of reduced blood loss during orthognathic surgery has been reported in which quantification of blood flow to oral tissues in humans is measured using the Doppler technique.[7] In a controlled study using this technique of quantification of blood flow to the maxillary gingival mucosa, a significant reduction in blood flow following hypotensive anesthesia was found.[8]

Initially, induced hypotension was also thought to decrease the surgical time due to improved visibility. Results of controlled studies[1,2,4] indicate that this belief is not true.

In many controlled[1–4] and uncontrolled studies[5,9–11] where induced hypotension had been employed, blood loss has been less than without hypotensive anesthesia. Again, no statistically significant difference was observed by Fromme et al.[6] However, their result may have arisen simply because their groups were small numerically. The data in the groups where hypotension was employed, in fact, showed a trend toward reduced blood loss.

The recent concern about hazards associated with blood transfusions, such as transmission of diseases like acquired immune deficiency syndrome and hepatitis, and the possibility of incompatibility, have increased the demand for techniques to prevent blood loss during surgery and thereby blood transfusions. In many studies in orthognathic surgery, where induced hypotension was employed there was either no necessity[10,11] or a decreased requirement[2,9] for blood replacement.

HISTORY

Deliberate hypotension to provide a bloodless field and better operative conditions for neurosurgery was first proposed by Harvey Cushing in 1917.[12] In 1943, Kohlstaedt and Page[13] experimenting with dogs described the use of arterial bleeding to produce hypotension resulting in a state of shock. In 1946, Gardner[14] introduced the concept of induced hypotension during anesthesia using arteriotomy as the technique to induce hypotension and produce a relatively bloodless surgical field. Subsequently, pentamethonium[15] was introduced to induce hypotension during anesthesia, soon to be followed by other ganglionic blocking drugs: hexamethonium,[16] trimethaphan,[17] and pentolinium.[18] Enderby stressed the importance of posture to induce hypotension.[15] Subsequently, deep anesthesia with volatile inhalational agents became favored by many.[19–22] In 1962, Moraca[23] first described the use of sodium nitroprusside to induce hypotension during anesthesia. Use of cardiac pacemakers to effect hypotension was introduced by Dimant in 1967.[24] Since then, nitroglycerin,[25] calcium-channel blocking agents,[26,27] short-acting β-adrenergic blockers,[3] purine compounds,[28,29] and prostaglandin E_1[30,31] have also been used.

The first use of hypotensive anesthesia with ganglionic blocking drugs in maxillofacial surgery was described by Enderby.[32] The first study on blood loss and hypotensive anesthesia in orofacial corrective surgery using sodium nitroprusside was reported by Schaberg in 1976.[5] Since then, induced hypotension during orthognathic surgery using nitroglycerin,[10] labetalol,[11] isoflurane,[2] and esmolol[3] has been reported.

PHYSIOLOGY

In order to use induced hypotension for the optimal benefit of the patient, it is necessary to have an understanding of the regulation of blood flow of vital organs. Even relatively short periods of unwanted hypotension, such as those associated with "shock," may be followed by irreversible organ damage. In this situation, the severe decrease in organ blood flow is accompanied by acid-base and metabolic changes. Controlled hypotension rarely results in damage, however, because organ blood flow is normally well maintained.

Richly perfused tissues, such as the brain, heart, liver, and kidneys exhibit autoregulation of their own blood supply through mechanisms related to the intrinsic elasticity of the vascular smooth muscle and vasodilator substances produced in the metabolically active tissues. That is, they maintain their perfusion over a wide range of pressure changes, and it is only when the pressure decreases to relatively low values that adequate perfusion cannot be maintained. This critical pressure varies from vessel to vessel, organ to organ, and probably from individual to individual.

Central Nervous System

Normally, cerebral blood flow remains constant over a mean arterial pressure (MAP) range of 60 to 150 mm Hg.[33] In chronically hypertensive patients, the autoregulatory curve is shifted to the right, and in whom the blood pressure has been controlled by antihypertensive treatment, the curve tends to shift back towards normal.[34]

Volatile anesthetic drugs attenuate or abolish the autoregulation of cerebral blood flow in a dose-dependent manner in the following order: halothane > enflurane > isoflurane.[35] The relative potency of these agents to decrease tissue metabolism is in the reverse order.[36] Decreases in the arterial carbon dioxide tension ($PaCO_2$) causes cerebral vasoconstriction. For every millimeter decrease in $PaCO_2$, the cerebral blood flow decreases by 2% in normotensive subjects.[37] This effect is either attenuated[38] or abolished[39,40] during hypotension, depending on the hypotensive agent. With isoflurane, the decrease in cerebral blood flow appears to be less than or equal to decrements in cerebral oxygen demand regardless of whether the patient is hypocapnic.[41]

Vasodilators such as sodium nitroprusside and nitroglycerin attenuate the autoregulation of blood flow in a similar manner to that of volatile agents.[36] Animal data suggest that cerebral metabolism and cerebral function are preserved during hypotension with hypocapnia in the following order: isoflurane > nitroprusside = nitroglycerin > trimethaphan.[42–44]

If the reduction in cerebral blood flow exceeds the reduction in the cerebral metabolic requirement for oxygen, cerebral ischemia may develop. When cerebral blood flow is reduced by 40% to 50% below control values, ischemic changes appear in the electroencephalogram (EEG), and below 60% the EEG becomes isoelectric.[45]

Elevation of the head during hypotensive anesthesia can aggravate the decrease in cerebral perfusion pressure. The perfusion pressure decreases by 2 mm Hg for every 2.5 cm the head is raised above the point of monitoring.[46,47]

Respiratory System

A head-up position in a patient decreases the apical perfusion of the lungs due to gravity, thus increasing dead space.[48] Accordingly, the $PaCO_2$ may rise. Induced hypotension may also decrease pulmonary artery pressure, increase blood flow through dependent regions of the lungs, and inhibit the hypoxic pulmonary vasoconstrictive effect, thereby increasing the intrapulmonary shunt and the $PaCO_2$.[49] This inhibition occurs with nitroprusside, nitroglycerin, and calcium-channel blockers, and to a lesser extent with isoflurane.[50,51]

The end-tidal carbon dioxide tension ($EtCO_2$) is commonly monitored during hypotensive anesthesia. It must be remembered that the gradient between the $PaCO_2$ and the $EtCO_2$ may increase significantly during hypotensive anesthesia due to the above factors.[52] To maintain normocarbia, it may be helpful to perform frequent $PaCO_2$ measurements.

The arterial oxygen tension (PaO_2) may be reduced during hypotension for the same reasons described for the $PaCO_2$. Thus, it is essential to maintain the oxygen saturation within normal limits, which may necessitate giving more than the normal amount of oxygen during hypotensive anesthesia. However, 100% oxygen is not preferable during hypotension, as this may cause vasoconstriction, especially in the brain.

Cardiovascular System

Even at rest, cardiac muscle extracts most of the oxygen delivered to it. Consequently, any increase in myocardial oxygen demand requires a parallel increase in coronary artery blood flow. Hypotensive anesthesia may substantially decrease coronary blood flow. However, it simultaneously decreases myocardial oxygen demand, due to the reduction in afterload (usually) and/or preload (sometimes). Furthermore, the coronary arteries dilate in response to the accumulation of metabolic vasodilator substances in the myocardium, thus ensuring an adequate blood flow to the myocardium. Hypotension with a normal or slow pulse is more beneficial than one with tachycardia. Tachycardia will increase the oxygen demand and shorten diastole, thus decreasing blood flow to the left ventricular subendocardium.

Coronary blood flow is rarely compromised in pediatric patients.[45] Factors that increase myocardial oxygen demand, such as tachycardia, should rarely cause myocardial ischemia even when the child is hypotensive. In patients with coronary artery obstruction, vasodilators used for hypotension may induce unfavorable intramyocardial blood flow redistribution as a consequence of resistance vessel dilatation, resulting in regional poststenotic hypoperfusion (the "steal" phenomenon) and possibly myocardial ischemia.[52]

Renal System

Decreases in renal blood flow stimulate the renin-angiotensin system. When the MAP falls below 75 mm Hg, the glomerular filtration rate falls.[53] Opioid analgesics and probably most inhalational agents stimulate secretion of antidiuretic hormone.[54] All these factors result in oliguria during hypotensive anesthesia. However, following termination of hypotensive anesthesia, urine formation rapidly recovers, provided the patient is well hydrated.[55]

Hepatic System

In patients with normal liver function, there are no reports of reduced liver function attributable to hypotensive anesthesia. The technique has been used successfully in

selected patients to reduce blood loss during operations for lienorenal shunts.[56]

BLOOD PRESSURE GOAL

Since the aim of hypotensive anesthesia is to reduce blood loss and provide an easily visualized surgical field, the degree of reduction should depend on each individual patient and clinical situation. The hypotension should be considered satisfactory when bleeding appears to be minimal and organ perfusion adequate. In theory, as long as the MAP exceeds the sum of the colloid osmotic pressure and the venous pressure, the circulation should be adequate for tissue needs. Although a pressure of 32 mm Hg should be sufficient theoretically, in practice it is probably below the safe limit due to the specific blood flow requirements of different organs and the possibility of disease and other causes of altered circulation.[57]

In patients undergoing cerebrovascular surgery, somatosensory evoked potentials and the redox potential of cytochrome a, a_3 in the mitochondria of cerebral cortical cells indicate that it is still possible to maintain cerebral metabolism at a functional level with a MAP between 40 and 60 mm Hg.[58] However, below a MAP of 40 mm Hg, deterioration of cerebral metabolism occurs, which, if not corrected, results in irreversible brain damage.

In orthognathic surgery, a decrease of MAP to between 50 and 65 mm Hg significantly reduced blood loss.[2,3,10,11] If the MAP was maintained at 70 mm Hg or above,[1,2] blood loss was similar to that of patients not receiving hypotensive anesthesia. However, those patients whose blood pressure was reduced by 20% or more from baseline exhibited a significant decrease in blood loss irrespective of the absolute blood pressure.[1,5]

Hypotensive anesthesia should be induced in relation to the patient's preoperative blood pressure rather than to a specific target pressure and should be limited to that level necessary to reduce bleeding in the surgical field and in duration to that part of the surgical procedure deemed to benefit by it. It is suggested that inducing hypotension to a MAP 30% below a patient's usual MAP, with a minimum MAP of 50 mm Hg in ASA Class I patients and 80 mm Hg in the elderly, is clinically acceptable.[52,58]

CONTRAINDICATIONS

Contraindications to the use of hypotensive anesthesia are listed in Table 1. Most contraindications are relative, depending on the type of surgery, the individual patient, the knowledge base and skill level of the anesthetist, and the drug or technique to be used. Absolute contraindications include known drug allergy, inability to monitor the patient adequately, and unfamiliarity with the technique.

Table 1. Contraindications to the Use of Hypotensive Anesthesia

Anesthetist limitations
  Lack of understanding of the technique
  Lack of technical expertise
  Inability to monitor the patient adequately
Patient limitations
  Cardiac disease
  Diabetes mellitus
  Gross anemia, hemoglobinopathies, polycythemia
  Hepatic disease
  Intolerance to the drugs available to produce hypotension
  Ischemic cerebrovascular disease
  Renal disease
  Respiratory insufficiency
  Severe systemic hypertension

MORBIDITY AND MORTALITY

In a large postal survey conducted in 1955, 96 deaths were reported in 27,930 cases of induced hypotension during anesthesia.[59] Over 50% of the deaths were related to decreased blood flow to the vital organs (eg, brain, heart, and kidneys). Other causes included reactionary hemorrhage (8), high-spinal anesthesia (5), and isolated cases of arterial air embolism, aortic-femoral thrombosis, pulmonary infarction, pulmonary edema, persistent hypotension, and excessive heparinization. In a separate study of 9,107 hypotensive anesthetics conducted between 1950 and 1960, nine deaths (0.1% mortality) were reported.[60] Of these, six were probably attributable to the technique. A report in 1959[61] describes a death following middle cerebral artery thrombosis in a patient who received hypotensive anesthesia, and another in 1974[21] attributes a death due to extensive cerebral and cerebellar infarction. Finally, a significantly higher mortality after hypotensive anesthesia was noted in patients with a history of cerebrovascular disease (3 out of 40 cases) than in patients with no history of cerebrovascular disease (2 out of 960 cases).[62]

Cerebrovascular System

In the aforementioned report of 1955,[59] 29 patients suffered cerebral thrombosis, of which 18 died. One case of hemiplegia was recorded in the series performed between 1950 and 1960.[60] Additional cases of middle cerebral artery thrombosis, hemiplegia, and severe cerebral and cerebellar infarction have also been reported.[21,61] The survey in 1961[62] reported 3 out of 40 cases who developed cerebral thrombosis as an extension of their existing cerebrovascular disease.

Although mental changes are common in the elderly following hypotensive anesthesia, they also occur in the absence of hypotensive anesthesia.[63]

Cardiovascular System

Mild coronary ischemia may occur during induced systolic hypotension below 60 mm Hg.[64] Patients with a previous history of hypertension are more susceptible to ischemia. Furthermore, rapid hypotension may be accompanied by an earlier onset of ischemic changes in the electrocardiogram (ECG).[65] In the 1955 series,[59] 18 cases of myocardial infarction were reported, of which eight died. Additionally, 22 cardiac arrests and 36 cardiovascular collapses were noted, with 14 dying. In a report in 1961[66] of 1,000 elderly patients who underwent hypotensive anesthesia, seven suffered myocardial infarction. Three cases of retinal artery thrombosis cases were also listed in the 1955 series.[59]

Due to the long action[59] or toxicity[67] of some hypotensive agents, persistent hypotension following hypotensive anesthesia has been reported. Reactionary hemorrhage can also occur following hypotensive anesthesia as the blood pressure reverts to normal or overshoots to a higher level in the immediate postoperative period. Such hemorrhage occurred in 243 patients described in the 1955 study,[59] of which eight died from this complication. In a subsequent prospective study,[68] postoperative bleeding was reported in 10.8% of patients undergoing thoracotomy, but the incidence was similar in those who did not have hypotensive anesthesia.

Other Systems

Two deaths attributed to hypoventilation were reported in the 1950 to 1960 series.[60] Anuria was recorded in 62 cases and oliguria in 54 cases of the 1955 review.[59] Nine of these patients died.

Skin Necrosis

Necrosis of the skin with ulcer formation can occur after prolonged hypotensive anesthesia from pressure-induced hypoperfusion. Common sites are the tip of nose (due to the pressure of the endotracheal tube or nasogastric tube) and pressure areas in the sacral region with the patient in the reverse Trendelenberg position. Recently, there was a report[69] of a finger injury from pressure of a finger probe (pulse oximeter) in a patient who had received hypotensive anesthesia. In a similar manner, thermal burns may appear in sacral areas when patients are placed on warming blankets during hypotensive anesthesia.[70]

Cyanide Poisoning

Large doses of nitroprusside administered to effect hypotension can result in cyanide poisoning, which manifests as metabolic acidosis, persistent hypotension, and tachycardia.[71–75] In some cases it has been fatal.[73–75]

Overall Risk

The validity of conclusions drawn from early retrospective surveys is limited. More recent reports[70,76] using control groups have been unable to show significant differences in morbidity and mortality attributable to induced hypotension during anesthesia. This is probably due to the more sophisticated modern monitoring techniques and better understanding of the physiology of respiratory, cardiovascular, and cerebrovascular systems and the pharmacology of anesthetic agents and hypotensive drugs.

METHODS OF HYPOTENSIVE ANESTHESIA

Since blood pressure is determined by the cardiac output and systemic vascular resistance, blood pressure can be lowered by decreasing the peripheral vascular resistance (afterload) and/or by lowering cardiac output (Table 2). A decrease in peripheral vascular resistance is obtained by causing vasodilatation of the resistance vessels. Cardiac

Table 2. Strategies for Inducing Controlled Hypotension

Category	Strategy	Examples
Decrease cardiac output	Reduce blood volume	Arteriotomy
	Dilate capacitance vessels	Nitroglycerin
	Decrease cardiac contractility	Inhalation anesthetics (eg, halothane), β-adrenergic blockers (eg, esmolol)
	Decrease heart rate	Inhalational agents, β-adrenergic blockers
Decrease peripheral vascular resistance	Block autonomic ganglia	Methonium compounds, pentolinium, trimethaphan
	Block α-adrenergic receptors	Phentolamine, labetalol
	Relax vascular smooth muscle	Direct-acting vasodilators (eg, nitroprusside), calcium-channel blockers (eg, nicardipine), purines (eg, adenosine), prostaglandin E_1, inhalational agents (eg, isoflurane)

output can be lowered by reducing venous return (pre-load), the heart rate, myocardial contractility or a combination of these factors. Inducing hypotension purely by a reduction in cardiac output is not ideal, however, because an adequate cardiac output is crucial for maintaining blood flow to the tissues. The circulation must be sufficient to supply oxygen and energy substrates to the tissues and to remove metabolic waste products before they can accumulate sufficiently to cause damage.

The final effect of hypotensive anesthesia on cardiac output will depend on the interactions among the after-load, preload, myocardial contractility, and heart rate. This balance is delicate and may be disrupted by intrinsic and extrinsic factors interacting with other homeostatic mechanisms. Such factors include the patient's clinical state, the administration of additional drugs, and the ventilatory pattern. To achieve the desired level of hypotension, maneuvers such as altering the position of the patient, adjusting the airway pressure, or adding other hypotensive drugs to complement the activity of the primary hypotensive agent can be used.

Once hypotension is induced, the required blood pressure to minimize blood loss may be maintained by adjusting the amount of the hypotensive agent administered, either manually or automatically by a self-tuning adaptive control device.[77,78] In the latter method, cardiovascular parameters are monitored electronically, with data being continuously transferred to a microcomputer. According to a preset algorithm based on the age and weight of the patient, the computer then controls the infusion of the hypotensive agent to maintain the blood pressure within the target range.

Pharmacological Agents

The ideal agent for inducing deliberate hypotension during orthognathic surgery would allow easy administration, a predictable effect, rapid onset and recovery, quick elimination with no toxic metabolites, and minimal alteration in blood flow to vital organs. At present, no perfect agent exists. Many pharmacological agents have been used to induce hypotension during orthognathic surgery. In addition, there are a number of drugs that have been used for induced hypotension in other types of surgery.

Ganglionic Blocking Drugs. These drugs block the ganglia of the autonomic nervous system, thus inhibiting both sympathetic and parasympathetic outflows. The hypotensive response results from blockade of sympathetic tone to both arteries and veins. Ganglionic blockade also affects the parasympathetic fibers to the heart, eye, gastrointestinal tract, bladder, and salivary glands, resulting in tachycardia, mydriasis, cycloplegia, decreased gastrointestinal mobility, urinary retention, and xerostomia.

Many of these changes are undesirable and limit the use of these drugs as hypotensive agents.

Methonium compounds. Pentamethonium and hexamethonium have been used to induce hypotension.[16,17] The latter has a more predictable action. However, both cause tachycardia, and fit young patients show tachyphylaxis.

Pentolinium. Pentolinium is five times as potent as hexamethonium and rarely leads to tachycardia because sympathetic fibers are more effectively blocked than parasympathetic fibers. The initial fall of blood pressure and the subsequent recovery of normal pressure after termination of the drug are slower than with hexamethonium.[18]

Trimethaphan. The primary ganglionic blocking drug still used for hypotensive anesthesia is trimethaphan camsylate. In addition to its ganglionic blocking action, trimethaphan directly relaxes arterioles and causes the release of histamine, which further enhance the hypotensive effect.[79] Trimethaphan may be given in intermittent doses of 10 mg of a 1% solution or more commonly by an infusion of a 0.1% solution in normal saline.[80] The blood pressure begins to decrease after 4 min, and the peak effect occurs within 10 min.[81] Hypotension depends on the speed of the drip; after the drip is stopped, recovery is moderately rapid. Trimethaphan has a short half-life (1 to 2 min) resulting from its rapid inactivation by plasma cholinesterase and subsequent renal excretion.

Trimethaphan can cause severe hypotension in arteriosclerotic patients, interferes with the heat-regulating mechanism, causing hypothermia after long operations, and reduces the need for anesthesia once a low pressure has been established.[82] Younger robust patients may prove resistant to its hypotensive action. Halothane is often used as an adjuvant to reduce the development of tachycardia.[70] The development of tachyphylaxis may be a problem, and the maximum recommended dose is 100 mg in the first 15 min and a total dose of 1 g.[83] Other potential problems include histamine release and potentiation of neuromuscular blockade.[84] Histamine release can theoretically dilate cerebral blood vessels and increase intracranial pressure. Direct cerebral toxic effects following trimethaphan have been reported. High brain lactate concentrations suggesting increased glycolytic activity, EEG burst suppression, and slowing of high voltage waves[85] have been reported at a MAP of 50 mm Hg. In addition, animals receiving trimethaphan exhibited signs of cerebral ischemia, which did not occur with other agents at comparable levels of hypotension.[86]

α-Adrenergic Blocking Agents. A number of agents possess the ability to block α-adrenergic receptors. Drugs used for this purpose range from agents classified

as α blockers to those in which α blockade is normally regarded as an undesired side effect.

Phentolamine. Phentolamine is a short-acting α-adrenergic receptor blocking agent. Its action is rapid, with peak effects occurring within 2 min. Its action lasts 10 to 15 min. Phentolamine has a powerful vasodilating effect. As a result of reflex sympathetic stimulation of the heart, tachycardia may become quite prominent. It is usually given in 2- to 5-mg intravenous boluses until adequate blood pressure control is obtained. Phentolamine can also be administered as an infusion.[52]

Labetalol. Labetalol is an α- and β-adrenergic receptor blocking agent. It is 4 to 8 times more potent at β than α adrenoceptors.[87] Thus, it reduces the blood pressure by reducing the peripheral vascular resistance while preventing a reflex increase in heart rate. It is 6 to 10 times less potent than phentolamine at α-adrenergic receptors, 1.5 to 4 times less potent than propranolol at β_1 receptors, and about 11 times less potent on β_2 receptors.

Labetalol can be given in intermittent bolus doses or by infusion. Its action is prompt, with peak effect occurring within 5 min. Although its half-life is relatively long at 4 hr,[11] the clinical effect of induced hypotension appears to last less than 30 min. The drug exhibits remarkable hypotensive synergism with inhalational agents, such as halothane[88] and isoflurane.[52] It appears to be less potent in reducing the blood pressure during neurolept anesthesia.[89] Advantages appear to be readily controllable hypotension, avoidance of tachycardia and tachyphylaxis, and avoidance of increased intracranial pressure and rebound hypertension.[90] A disadvantage is that it will mask the response to acute blood loss even in the postoperative period because of its long half-life.[91] Contraindications include heart failure, bradycardia, hypovolemia, and atrioventricular block. In orthognathic surgery, labetalol has been used successfully to induce hypotension and significantly decrease blood loss and the need for blood transfusion.[11]

Antipsychotic Agents. Chlorpromazine and droperidol, antipsychotic agents with significant α-adrenergic blocking properties, have been used to control blood pressure during anesthesia. Due to their long half-lives, they are usually given for premedication in patients undergoing controlled hypotension, thus acting as adjuncts to other hypotensive agents.[45]

Direct-Acting Vasodilators. Drugs that relax smooth muscle directly include nitroprusside, nitroglycerine, and hydralazine.

Nitroprusside. Nitroprusside is one of the most widely used agents for inducing hypotension in a variety of procedures, including orthognathic surgery.[1,5,6,83] It was first used in anesthesia for this purpose in 1962.[24] It acts directly on the vessel walls by interacting with membrane-

bound sulfhydryl groups.[92] Nitric oxide is released from the drug molecule, which then diffuses across the cell membrane to stimulate guanylate cyclase. The resultant increase in guanosine 3',5'-monophosphate inhibits the contractile mechanism. A blockade of the intracellular release of calcium facilitates the relaxation. Nitroprusside mainly acts on the arterioles, or resistance vessels, and less on the venules, or capacitance vessels.[93] This differential effect reduces the arteriolar-venular pressure gradient. As a result, tissue oxygenation may fall during nitroprusside infusion even though the PaO_2 remains normal.[94] Sensitivity to vasodilatation from nitroprusside increases with age, probably due at least partly to an age-related resistance of cardiac adrenergic receptors to catecholamine stimulation.

Nitroprusside is available in bottles, each containing 50 mg of the drug in powder form. The agent can be dissolved in 5% dextrose or normal saline. The solution should not be exposed to light because it breaks down, and the container is usually wrapped with aluminum foil. If the solution attains a blue color, indicative of the breakdown of nitroprusside, it should be discarded.[95] It is given by intravenous infusion as its half-life is about 2 min.[96] Its action is rapid, appearing within 1 min. The degree of hypotension can be titrated against the infusion rate. The usual dose range of nitroprusside is 0.5 to 10 μg/kg-min. If an adequate reduction in blood pressure is not obtained within 10 to 15 min at the highest recommended dose, the infusion should be stopped to prevent cyanide toxicity.[91] Reversal is spontaneous with the termination of infusion.

Metabolism of nitroprusside occurs when it comes in contact with either tissue or red blood cell sulfhydryl groups.[97] Inside red blood cells, cyanomethemoglobin and an unstable tetracyano compound are formed. Cyanide released from this unstable compound combines with thiosulfate to form thiocyanate. This reaction is catalyzed by the liver and kidney enzyme rhodanase. Cyanide also combines with hydroxocobalamin producing cyanocobalamin. Both thiocyanate and cyanocobalamin are water soluble and are excreted in the urine. Some hydrogen cyanide is exhaled. Cyanide can also react with mitochondrial cytochrome oxidase to form a cytochrome oxidase-cyanide complex, which inhibits cellular respiration and results in cytotoxic hypoxia. A high level of this complex can lead to metabolic acidosis and death.[84] Nitroprusside should not be given to patients with Leber's optic atrophy, tobacco amblyopia, vitamin B_{12} deficiency, or liver or renal failure, as these conditions affect normal cyanide metabolism.[95]

Adverse effects of nitroprusside include cyanide toxicity. Metabolic acidosis is an indirect indicator of cyanide toxicity.[52] Additional signs of toxicity include tachycardia and persistent severe hypotension even after withdrawal

of the drug.[91] The blood cyanide concentration is related to the total dose of nitroprusside administered per unit time. Correlation of blood cyanide with subsequent metabolic acidosis has led to decreasing recommendations for safe limits of sodium nitroprusside, the latest recommended safe dose being 0.5 to 0.7 mg/kg in 2 to 3 hr.[97] If cyanide toxicity is suspected, the infusion should be immediately stopped. Sodium nitrite, 5 mg/kg, can be injected slowly intravenously or amyl nitrite can be given by inhalation. Nitrites form methemoglobin, and cyanide combines preferentially with methemoglobin to produce cyanomethemoglobin, preventing the cytochrome oxidase-cyanide tissue complex from forming. In case of severe toxicity, sodium thiosulfate 150 mg/kg can also be given intravenously. This acts as a sulfur donor and converts cyanide to thiocyanate through the rhodanase pathway.[52] If no improvement occurs, 20 mL (300 mg) of cobalt edetate should be injected at the rate of 1 mL/sec.[95] Although cobalamins normally present in the food can combine with cyanide to produce water-soluble cyanocobalamin, the efficacy of hydroxocobalamin in reversing actual sodium nitroprusside-induced cyanide toxicity remains to be demonstrated.[91]

Tachyphylaxis or increasing dose requirements to maintain hypotension has been reported with sodium nitroprusside. In these patients, the blood cyanide concentrations are higher and may or may not be accompanied by metabolic acidosis. Acute tolerance may result from a decreased responsiveness of the guanylate cyclase system to nitric oxide. Resistance may also occur due to increased plasma renin, angiotensin II, and catecholamine activity. If tachyphylaxis occurs, the infusion should be immediately stopped, as it can lead to cyanide toxicity.[91]

Rebound hypertension of 20 mm Hg or greater of systolic blood pressure lasting for 30 min following abrupt termination of nitroprusside infusion has been reported.[98] Increased renin secretion associated with the hypotension results in production of angiotensin I and angiotensin II. The increase in blood pressure is due to angiotensin II. This response can be attenuated by tapering the infusion over 30 to 45 min, using agents such as propranolol to inhibit renin secretion,[91] or giving angiotensin-converting enzyme inhibitors such as captopril[99,100] or enalaprilat[101] to inhibit production of angiotensin II.

Nitroprusside can also decrease the platelet concentration,[102] inhibit platelet aggregation,[103] and impair pulmonary hypoxic vasoconstriction.[49]

In order to reduce the dose of nitroprusside used, thereby preventing cyanide toxicity, various agents can be used to augment the action of nitroprusside. Trimethaphan provides an excellent example. Both drugs are dissolved in 5% dextrose in the proportion to be infused. Nitroprusside/trimethaphan ratios from 1:10 to 1:2.5 have been employed with success.[104–109] Nitroprusside and esmolol can also be used together to induce hypotension.[110,111] Esmolol infusion causes dose-dependent reductions in the nitroprusside requirement by decreasing heart rate, myocardial contractility, and renin activity. The angiotensin-converting enzyme inhibitors captopril and enalaprilat provide a similar additive effect.[99–102] They decrease the rise in endogenous vasoconstrictors due to stimulation of the renin-angiotensin system during nitroprusside infusion.

In orthognathic surgery when nitroprusside was used to reduce pressure to a predetermined MAP, blood loss was not significantly reduced compared to that in normotensive patients.[1,3,6] However, when the MAP was reduced by 20% or more from the preoperative value, blood loss was significantly reduced.[1,5]

Nitroglycerin. Intravenous nitroglycerin has been used successfully to induce hypotension during orthognathic surgery.[10,112] It acts directly on the vascular smooth muscle[92] in a similar manner to that of nitroprusside. However, its action is predominantly on capacitance vessels, resulting in decreased venous return to the heart, and therefore a reduced stroke volume and cardiac output.[113]

Nitroglycerin is supplied in 20-mL glass ampoules containing 10 mg of drug. In this form it is stable in light. It may be adsorbed by plastic, hence the drug should be infused in glass bottles or high-density polyethylene syringes and tubing[114] and is not diluted before injection.[91] It is given as an intravenous infusion, since its half-life is about 2 min.[52] The infusion is started at a rate of 1 to 2 μg/kg-min and increased to achieve the desired mean arterial pressure.[91] Its action is rapid, appearing within 1 min. There is no upper limit to the rate of infusion as there are no toxic metabolites reported. Usually with 2 μg/kg-min, a good hypotensive response is obtained. However, especially in young patients, it may be impossible to achieve the desired degree of hypotension with nitroglycerin.[52] Reversal is spontaneous with the ending of the infusion.

Metabolism of nitroglycerin occurs principally in the hepatic[115] and pulmonary vascular beds.[116] Unlike nitroprusside, no significant inactivation occurs in the peripheral blood and no toxic metabolites are produced.[52]

Arterial and tissue oxygen tensions remain unchanged,[94] probably because of the persistent pressure gradient between the arteriolar and the venular sides of the microcirculation and the lesser degree of diversion of blood through arteriovenous shunts during nitroglycerin-induced hypotension, as compared to that of nitroprusside. An additional advantage over nitroprusside is the absence of rebound hypertension.[91]

Hydralazine. Hydralazine has been used intravenously to produce hypotension during anesthesia.[117–119] It acts

directly on vascular smooth muscle, mainly on the arterioles or resistance vessels, at least in part through the release of nitric oxide. Reflex tachycardia commonly accompanies the hypotension. Onset of the hypotensive effect may take up to 20 min.[47] As with nitroprusside and nitroglycerin, it should not be used in patients with low intracranial compliance.[91]

Calcium-Channel Blockers. Nicardipine,[120-125] nifedipine,[52] diltiazem,[126] and verapamil[27] have all been used to produce hypotensive anesthesia. Agents other than verapamil vasodilate resistance vessels but have no effect on the capacitance vessels. With clinical doses they maintain myocardial contractility and cardiac output with no increase in heart rate or only a modest tachycardia.[28] However, verapamil has a significant negative inotropic effect, a lesser vasodilating effect, and should be reserved for its antiarrhythmic and antianginal actions.

Nicardipine is popular as it is sufficiently water soluble to be administered in intravenous solutions. When 0.5 mg of nicardipine is given intravenously, the maximal effect comes on in 2.5 min.[52] Its distributional half-life is 14 min and terminal half-life is 4.75 hr.[121] Clearance is mainly by hepatic metabolism to inactive metabolites. Compromised renal function is a potential complication of nicardipine.[52] Despite normal left-heart filling pressures and cardiac output, blood is shunted away from the renal vascular bed, producing a clinical picture consistent with prerenal failure. Once the drug is withdrawn, patients recover renal function rapidly. Careful titration of the infusion to attain the desired level of hypotension should be carried out, as excessive decreases may not be quickly reversed.

Purines. Adenosine and adenosine triphosphate are potent vasodilators, and both have been used to induce hypotension during anesthesia.[28,29,127-134] Adenosine triphosphate is rapidly decomposed to adenosine in the blood, and the vasodilatation it produces has been ascribed to adenosine.[135] Adenosine stimulates specific receptors on the vessel walls of arterioles to produce vasodilatation.[128] A lack of effect on capacitance vessels may be associated with the rapid tissue metabolism of adenosine (half-life: 10 to 20 sec)[52] resulting in most of it being metabolized before reaching the veins. In contrast to nitroprusside and nitroglycerin, the decrease in peripheral vascular resistance is accompanied by an increase in cardiac output without an increase in the heart rate.[128] As it has no positive inotropic action on the myocardium,[136] this effect is probably due to its selective ability to reduce peripheral vascular resistance. In doses higher than used to induce hypotension, adenosine can produce bradycardia by a direct action on the sinus node[137] and the conducting system of the heart, as well as by inhibition of

cardiac sympathetic neurotransmission.[138] Adenosine dilates the coronary blood vessels, increasing the coronary blood flow.[130-132]

Adenosine can be infused in an isotonic saline solution at a rate of 60 to 350 μg/kg-min.[130-132,134] Hypotension occurs rapidly, and a stable blood pressure with easy control is obtained. Switching off the infusion brings back the blood pressure without rebound hypertension. Rebound hypertension and tachyphylaxis do not occur because adenosine inhibits renin secretion[131] and norepinephrine release[139] by a presynaptic effect.[140]

Adenosine is metabolized to inosine or is taken up by the cells. Inosine is converted to hypoxanthine, which is oxidized to uric acid.[141]

Because large doses of adenosine may have to be used to produce hypotension, uric acid may accumulate as a metabolite, a problem for patients with gout.[52] Adenosine should also be used with caution in patients suffering from myocardial ischemia as it may cause the "steal phenomenon," shifting coronary blood flow away from ischemic areas.[130] Adenosine can increase the cerebral blood volume and intracranial pressure.[142] If adenosine triphosphate is used, considerable phosphate is released, and the phosphate binding of calcium and magnesium can lead to dysrhythmias.[143] Thus, it is better to use adenosine rather than adenosine triphosphate to induce hypotension.

In order to reduce the dose of adenosine required to produce hypotension and thereby reduce the amount of uric acid formed, dipyridamole, a drug that inhibits adenosine uptake by cells, can be administered concomitantly.[144]

Prostaglandin E₁. Prostaglandin E_1 is one of the more recently used agents for inducing hypotension during anesthesia.[125,145-147] It is a potent vasodilator[148] of systemic and pulmonary vascular beds. Its inotropic effect[149,150] on the heart increases the cardiac output, an effect aided by the peripheral vasodilation and decreased afterload. Following infusion of PGE_1, no significant increase in heart rate is observed despite a significant fall in arterial pressure,[147,151] probably due to the attenuation of the baroreflex in response to the induced hypotension. However, the arterial baroreceptor response to acute hypovolemia during hypotensive anesthesia is better maintained than with nitroprusside and trimethaphan.[32] Prostaglandin E_1 also maintains the oxygen supply to the myocardium[151] and is antiarrhythmic.[152,153] In patients without decreased intracranial compliance, it maintains cerebral blood flow, autoregulation, and normal jugular venous oxygen tensions.[154] At physiological and pharmacological concentrations, it does not affect clotting time, bleeding time, or adenosine diphosphate-induced platelet aggregation.[151] Prostaglandin E_1 increases renal

blood flow, urine formation, and sodium excretion during hypotension under general anesthesia.

Inhalational Agents. The inhalational agents halothane,[1,9,21,155–158] enflurane,[6,22,23] isoflurane,[2,159–161] and desflurane[162,163] have been used to induce hypotension during anesthesia.

Hypotension with halothane results primarily from myocardial depression. Although vasodilatation occurs in the skin, brain, and splanchnic vasculature, the peripheral resistance does not decrease significantly because of the increase in tone of skeletal muscle and renal arterioles.[164] Halothane is used for hypotensive anesthesia because of its ability to produce hypotension with a lack of or even suppression of tachycardia. The disadvantages of halothane are its direct myocardial depressant effect without decrease of peripheral vascular resistance, sensitization of the myocardium to the arrhythmogenic effect of catecholamines, and the possibility of halothane hepatitis.[112] With deep halothane anesthesia, significant oozing of blood despite hypotension has been reported.[165]

Hypotension with enflurane is caused by a combined decrease in peripheral vascular resistance and myocardial depression.[164] Enflurane is also less arrhythmogenic when used in conjunction with catecholamines. However, it may precipitate epileptiform convulsions in those who are susceptible to it, especially in the presence of hypocarbia, and may produce renal damage in those with renal disease or in obese patients.[165] Controlled hypotension under deep enflurane anesthesia has produced no decrease in blood flow to the maxilla, mandible, or tongue and has even produced an increase in blood flow to the suprahyoid and masseter muscles.[166] Thus, deep enflurane anesthesia per se may not be beneficial to oral and maxillofacial surgery.

In equipotent doses, isoflurane produces rapid hypotension by decreasing peripheral vascular resistance without myocardial depression.[23,112] It also provides better myocardial perfusion than halothane or enflurane.[112] Although myocardial perfusion improves generally, in patients with coronary artery stenosis, coronary steal may occur.[52] With isoflurane, baroreflex activity is better maintained during hypotensive anesthesia.[21,112] This may result in tachycardia during controlled hypotension. Isoflurane has been used as the sole agent to induce hypotension during orthognathic surgery[2] and has significantly reduced blood loss and improved the quality of the surgical field.

Desflurane is a new volatile anesthetic agent whose cardiovascular effects have been reported to be similar to those of isoflurane.[159] It has been used for hypotensive anesthesia in dogs[160] and has decreased the blood pressure by reducing peripheral vascular resistance and car-

diac output. As yet, there are no reports of its use for induced hypotension in humans. It appears best to use inhalational agents as adjuvant drugs[8] for hypotensive anesthesia rather than using them as sole agents.

β-Adrenergic Blocking Agents. β-Adrenergic blocking agents are either used as the sole hypotensive agent[3,167] or as an adjunct[9,110,111] to other hypotensive techniques. In orthognathic surgery, stimulation of branches of the trigeminal nerve in turn stimulates the sympathetic nerve centers in the medulla, resulting in tachycardia and increased blood pressure.[168] β-Adrenergic antagonists attenuate this response. Furthermore, any drug that lowers the peripheral vascular resistance and decreases blood pressure will cause activation of baroreceptors and a reflex increase in the heart rate to compensate for the decrease. β-Adrenergic blocking agents help to block this response as well. They may also prevent tachycardia in response to hypoxia, hypocarbia, hypovolemia, and hypoglycemia. Caution should be exercised before administering them to patients with established right or left ventricular failure, hyperdynamic circulation in anemia, or heart block.[168]

Propranolol has enjoyed the longest use in hypotensive anesthesia.[50,169,170] Its hypotensive effect is believed to occur by the blockade of cardiac β adrenoceptors, inhibition of renin release, and a central action. After a test dose of 0.25 to 0.5 mg to evaluate the degree of response or any side effects, the drug can be given in similar increments until the desired response is obtained. As it is not a cardioselective β blocker, propranolol may cause bronchospasm by blocking β_2 receptors in susceptible patients.[168]

Metoprolol has also been used for hypotensive anesthesia.[171,172] The primary advantage over propranolol is that it is a selective β_1 blocker and is less likely to produce bronchospasm in susceptible patients.

Esmolol is a relatively new cardioselective β blocker available in 10 mg/mL, 100 mg/mL, and 250 mg/mL ampoules. It has a quick onset and a short duration of action.[173] It has a rapid distribution half-life (2 min) and an elimination half-life of only 9 min. Thus, it can be used in bolus doses or preferably as an infusion. Once the infusion is terminated, the blood pressure reverts to the original pressure within 30 min. It has successfully been used for controlled hypotension during anesthesia either alone[3,166] or in conjunction with another hypotensive agent acting peripherally.[110,111] It is metabolized primarily by esterases in the cytosol of red blood cells to an inactive metabolite and is safely eliminated in patients with hepatic or renal impairment.[174] Esmolol can significantly decrease the cardiac index, an effect opposite that of nitroprusside.[174]

Adjunctive of Agents

A number of drugs that are not used specifically to lower blood pressure intraoperatively nevertheless promote drug-induced hypotensive anesthesia. Chief among these are the neuromuscular blocking drugs and the opioid analgesics.

Neuromuscular Blocking Agents. Tubocurarine was the first neuromuscular blocker to be used in patients undergoing controlled hypotension during anesthesia. It produces a fall of blood pressure in its own right due, in part, to ganglionic blockade and histamine release.[175] Large doses of alcuronium and, to a lesser extent, atracurium, can also cause a drop in blood pressure through histamine release. Vecuronium is a primary example of a "pure" neuromuscular blocker, one that has no significant direct effect either on heart rate or blood pressure. Nevertheless, the blood pressure may decrease after vecuronium simply as a consequence of the neuromuscular blockade. The necessity for positive pressure ventilation tends to decrease venous return to the heart, an effect that is augmented by the loss of muscle tone in tissues surrounding the capacitance veins. Pancuronium, which produces tachycardia,[176] is an exception to the general rule that neuromuscular blockers facilitate hypotensive anesthesia.

Opioid Analgesics. Opioids decrease the doses of agents necessary to produce anesthesia and hypotension.[9] Certain opioids, such as meperidine and morphine can cause histamine release. More important, however, is the ability of opioids to attenuate sympathetic responses to stress.

Mechanical Maneuvers to Potentiate the Action of Hypotensive Agents

Positioning. The importance of correct positioning of the patient during controlled hypotension in anesthesia cannot be overemphasized.[14,46,47] Elevation of the site of operation allows easy drainage of venous blood from the site of surgery. Inclining the patient (raising the head) 15° to 25° off the horizontal plane facilitates pooling of blood in the dependent regions of the body, thus reducing venous return to the heart and the cardiac preload. Blood pressure is also reduced gravimetrically in the operating field. For each 2.5-cm elevation of the site above the heart, there is a 2-mm Hg fall in blood pressure.[46] The hypotensive effects of most of the hypotensive agents are potentiated by posture. Rapid changes in posture may be followed by rapid changes in blood pressure; thus, tilting the head down may be used to rapidly reverse excessive hypotension.

Positive Airway Pressure. Use of positive pressure ventilation decreases the venous return during the positive pressure phase.[177] This effect can be enhanced by increasing the inspiratory volume, prolonging the inspiratory time, and raising the positive end-expiratory pressure.[83,178] However, these manipulations not only cause a deleterious effect on the cardiac output and pulmonary perfusion, but also result in increased respiratory dead space. Increasing intrathoracic pressure can also decrease venous outflow from the cranium sufficiently to increase the cerebral blood volume and intracranial pressure. Thus, respirator manipulations to minimize venous return are usually not employed in controlled hypotension.

ANESTHETIC MANAGEMENT

Preoperative Management

The decision to induce hypotension is best taken preoperatively following examination of the patient. As a crucial prerequisite, the anesthetist conducting the hypotensive anesthesia must have a thorough knowledge of the technique that is to be performed. Appropriate patient evaluation and selection are also important for safe induced hypotensive anesthesia. Preoperative investigations including hemoglobin (Hb), urea, electrolytes, and ECG should be carried out. A minimum Hb of 10 g/dL should be safe in those undergoing hypotensive anesthesia.[45] Either in the ward before transport or in the operating room before anesthesia, arterial blood gas sampling may help provide a baseline for intraoperative or postoperative measurements. Various premedications, including anxiolytics, analgesics, α blockers (eg, droperidol, chlorpromazine), β blockers (eg, metoprolol),[172] and antihypertensives (eg, clonidine),[161,179] can assist the induction of hypotension during anesthesia. Vagolytic drugs are best avoided.

Intraoperative Management

Following preanesthetic monitoring, induction of anesthesia can be carried out in the usual manner. A stress-free induction and obtunding the increase in blood pressure and tachycardia to intubation will help set the stage for a smooth hypotensive technique. The endotracheal tube and any other tube placed through the nares should not exert undue pressure on the tip of the nose. A second intravenous line is preferable if the hypotensive drug is to be given as an intravenous infusion. During maintenance of anesthesia, a patient who is to undergo hypotensive

anesthesia during orthognathic surgery is usually ventilated with the help of neuromuscular blocking agents.

Posture. As mentioned previously, the patient should be positioned with the head elevated about 20° above the heart. Having the legs slightly elevated by flexing the table at the hips of the patient prevents the patient slipping down the table and prevents pressure sores in the sacral region during hypotensive anesthesia. Soft cotton wool pads for the sacral region and the feet, the regions which act as pressure points, will help to prevent skin necrosis.

Monitoring. Meticulous monitoring is essential for patient safety during hypotensive anesthesia.

Blood pressure. Intraarterial blood pressure monitoring during hypotensive anesthesia is recommended by many as it not only helps in getting immediate and often more accurate blood pressure data than can be obtained with noninvasive blood pressure monitors but also permits sampling for arterial blood gases, hematocrit, and other laboratory investigations. If noninvasive blood pressure monitoring is also to be used, attaching a blood pressure cuff to the same arm that is used for arterial cannulation will help check the accuracy of blood pressure recordings from the indwelling catheter. Noninvasive monitoring will also be helpful during periods of problems with arterial blood pressure monitoring. Although not the ideal, hypotensive anesthesia may be carried out without invasive blood pressure monitoring, especially when the procedure is short and techniques are used that are not likely to cause rapid swings in blood pressure.

Electrocardiogram. Monitoring of the V_5 lead of the ECG with an appropriate input filter, which is essential for ST-segment analysis, may give an indication of cardiac ischemia if it occurs and warn the anesthetist that the coronary blood supply is compromised.

Oxygen saturation. It is important to monitor oxygen saturation, as hypotension can cause a mismatch of ventilation and perfusion in the lungs as well as reduced blood flow to peripheral tissues. The pulse oximeter probe should not exert undue pressure on the finger tip.

End-tidal carbon dioxide. The measurement of the end-tidal carbon dioxide tension ($EtCO_2$) will give an indication of the $PaCO_2$ and will help prevent both hypo- and hypercarbia. However, the relationship between $PaCO_2$ and $EtCO_2$ changes with hypotension, so that arterial blood gas determinations also should be carried out intermittently to make sure that the $PaCO_2$ is within the desired range.

Temperature. Core temperature monitoring is important during controlled hypotension, because body heat dissipates more rapidly from dilated vessels. Lowered temperature may decrease the effectiveness of vasodila-

tors and increase the dose requirements if compensatory vasoconstriction occurs.

Central venous pressure. A greater hypotensive response will be exhibited by hypovolemic patients at the onset of controlled hypotension. Central venous pressure measurements will help in determining the adequacy of circulating blood volume at the start of hypotension and will help to maintain it during the period of controlled hypotension.

Urine volume. Urine output decreases during hypotensive anesthesia. However, some urine is formed. If the operation is to exceed 5 hr, a urinary catheter should be inserted. By measuring the urine output, it is possible to ensure that renal perfusion is maintained. Usually, once the hypotension is reversed, urine output reverts to normal.

Blood loss. The physiological response to blood loss may be lost during hypotensive anesthesia. Therefore, blood loss should be carefully estimated using swab weighing and measuring blood volume in suction bottles.

Cardiac output. The decrease in cardiac output during hypotensive anesthesia can be measured by the insertion of pulmonary artery catheters. The catheters can also help in monitoring the fluid status, left heart function, and mixed venous oxygen content.

Fluid Therapy. Proper fluid therapy is essential during hypotensive anesthesia. The aim of induced hypotension is to lower the MAP while maintaining adequate perfusion of all vital organs. Thus, preoperative fluid and electrolyte status must be assessed and corrected if necessary before anesthesia. During anesthesia, the fluid deficit acquired in the preoperative period because of fasting should be calculated and replaced during the first 1 or 2 hr. For maintenance, 5 to 6 mL/kg-hr of crystalloids should be infused. Blood loss must be carefully observed, and replacement carried out with either an equal amount of colloid or three times the amount in crystalloid. If the blood loss exceeds 20% to 25% of the patient's total blood volume, the loss should be replaced with blood. In operations where major blood loss is expected, it is preferable to insert a central venous catheter to ensure adequacy of the circulating volume.

Induction of hypotension should begin at the time of mucosal incision. That will give time to attain the required MAP before osteotomy. Once hypotension is induced, the required level of blood pressure to minimize blood loss may be maintained by adjusting the amount of hypotensive agent, either manually or automatically by self-tuning adaptive control.[77,78]

Hypotension should be carried out only to that level needed to reduce bleeding and only for that time of the surgery where it is of benefit in reducing significant blood loss.

Postoperative Management

After anesthesia with induced hypotension, adequate postoperative care with resuscitation facilities and experienced nursing staff is essential to prevent morbidity and/or mortality that can occur during this period. Postoperatively, attention should be given to airway maintenance, oxygenation, analgesia, monitoring, positioning, reactionary hemorrhage, and fluid balance. Persistent hypotension, which may be related to the positioning of the patient, a prolonged action of the hypotensive drugs, or both, may occur. Rebound hypertension, especially with inadequate analgesia, is also a concern during this period.

CONSIDERATIONS FOR FUTURE STUDIES

There are many deficiencies in the majority of the studies on hypotensive anesthesia carried out during orthognathic surgery. Results obtained from retrospective studies[5,9] are unreliable compared to those of prospective studies.[1–4,6,8,10,11] Control of the age group[4,10] and the physical status[2–4,10,11] is important, as different age groups and patients of different physical status react differently to hypotensive agents. Furthermore, lack of sufficient number of patients[6] results in inconclusive data. Orthognathic surgery consists of maxillary and mandibular surgery using different operative techniques. It is said that blood loss during maxillary osteotomies is greater than that of mandibular osteotomies and may vary with different techniques. A comparison should preferably be not of patients undergoing orthognathic surgery in general but should be specified to similar types of orthognathic surgery,[1–4] such as Le Fort I operations.[8] Many reported studies are uncontrolled.[5,9–11] To obtain valid results, controlled studies[1–4,6,8] are necessary. The lowering of blood pressure to a percentage range of the preoperative blood pressure appears to be more rational than to a range of specific target blood pressures.[1–3,6,8–11] The technique of induced hypotension and the hypotensive drug(s) used should be the same for all patients in the hypotensive group during comparison of normotensive and hypotensive anesthesia.[1–3,5,6,9–11] If more than one drug or technique is used, the results should provide comparisons of the different drugs and techniques. Assessment of the quality of the surgical field carried out blindly by the surgeons at frequent intervals is better[4] than an overall assessment at the end of surgery.[6] Preferably, the time of assessment should be stated.[4] Estimation of blood loss may vary from the true blood loss. Preoperative and postoperative hemoglobin[9] and hematocrit values[4,5,10] have been used to supplement the calculation of blood loss and appear to be useful. Further studies designed with the aforementioned considerations,

and if possible supplemented with the Doppler technique to quantify blood flow to the area of orthognathic surgery,[8] will be able to confirm the benefits of hypotensive anesthesia during orthognathic surgery.

In conclusion, hypotensive anesthesia is undoubtedly of great value in improving the quality of the surgical field during orthognathic surgery. Although autologous blood transfusion and normovolemic hemodilution may be acceptable alternatives to homologous blood transfusion, they do not constitute a universal replacement for homologous blood transfusion.[180] Reverse Trendelenberg position, sequential surgical site packing, keeping only the current site of operation exposed at any one time, injection of local anesthesia with epinephrine, and meticulous surgical technique with gentle tissue manipulation and use of cautery and vessel ties when appropriate are additional methods that help reduce blood loss. However, until satisfactory alternative methods are found to eliminate the need for homologous blood transfusion, it remains necessary to conduct hypotensive anesthesia during orthognathic surgery to prevent blood loss and transfusion therapy.

REFERENCES

1. Chan W, Smith DE, Ware WH: Effects of hypotensive anesthesia in anterior maxillary osteotomy. J Oral Surg 1980; 38:504–508.

2. Lessard MR, Trépanier CA, Baribault JP, Brousseau CA, Cote JJ, Denault PH: Isoflurane-induced hypotension in orthognathic surgery. Anesth Analg 1989;69:379–383.

3. Blau WS, Kafer ER, Anderson JA: Esmolol is more effective than sodium nitroprusside in reducing blood loss during orthognathic surgery. Anesth Analg 1992;75:172–178.

4. Precious DS, Bosco DA, Splinter W, Muir J: Induced hypotensive anesthesia for adolescent orthognathic surgery patients. J Oral Maxillofac Surg 1993;51(Suppl 3):94–95.

5. Schaberg SJ, Kelly JF, Terry BC, Posner MA, Anderson EF: Blood loss and hypotensive anesthesia in oral-facial corrective surgery. J Oral Surg 1976;34:147–156.

6. Fromme GA, MacKenzie RA, Gould AB, Lund BA, Offord KP: Controlled hypotension for orthognathic surgery. Anesth Analg 1986;65:683–686.

7. Dodson TB, Neuenschwander MC, Bays RA: Intraoperative assessment of maxillary perfusion during Le Fort I osteotomy. J Oral Maxillofac Surg 1994;52:827–831.

8. Bulloch SE, Fridrich KL: Capillary blood flow in the maxilla during hypotensive anesthesia for maxillary surgery. J Oral Maxillofac Surg 1993;51(Suppl 3):142–143.

9. Washburn MC, Hyer RL: Deliberate hypotension for elective major maxillofacial surgery: a balanced halothane and morphine technique. J Maxillofac Surg 1982;10:50–55.

10. Golia JK, Woo R, Farole A, Seltzer J: Nitroglycerin-controlled circulation in orthognathic surgery. J Oral Maxillofac Surg 1985;43:342–345.

11. McNulty S, Sharifi-Azad S, Farole A: Induced hypotension with labetalol for orthognathic surgery. J Oral Maxillofac Surg 1987;45:309–311.

12. Cushing H: Tumors of the Nervus Acusticus and the Syndrome of the Cerebellopontine Angle. Philadelphia, WB Saunders, 1917.

13. Kohlstaedt KG, Page IH: Hemorrhagic hypotension and its intra-arterial and intravenous infusion of blood. Arch Surg 1943;47:178–191.

14. Gardner WJ: The control of bleeding during operation by induced hypotension. JAMA 1946;132:572–574.

15. Enderby GEH: Controlled circulation with hypotensive drugs and posture to reduce bleeding in surgery: preliminary results with pentamethonium iodide. Lancet 1950;1:1145–1147.

16. Shackleton RPW: The reduction of surgical haemorrhage. Some observations on controlled hypotension with methonium compounds. Br Med J 1951;1:1054–1056.

17. Magill IW, Scurr CF, Wyman JB: Controlled hypotension by a thiophanium derivative. Lancet 1953;1:219–220.

18. Enderby GEH: Pentolinium tartrate in controlled hypotension. Lancet 1954;2:1097–1098.

19. Murtagh GP: Controlled hypotension with halothane. Anaesthesia 1960;15:235–244.

20. Prys-Roberts C, Lloyd JW, Fisher A, Kerr JH, Patterson TJS: Deliberate profound hypotension induced with halothane: studies of haemodynamics and pulmonary gas exchange. Br J Anaesth 1974;46:105–116.

21. Patel NJ, Patel BS, Paskin S, Laufer S: Induced moderate hypotensive anesthesia for spinal fusion and Harrington-rod instrumentation. J Bone Joint Surg 1985;67:1384–1387.

22. Bernard JM, Pinaud M, Maquin-Mavier I, Remi JP, Passuti N: Hypotensive anesthesia with isoflurane and enflurane during total hip replacement: a comparative study of catecholamine and renin angiotensin responses. Anesth Analg 1989;69:467–472.

23. Moraca P, Bitte EM, Hale DE, Wasmuth CE, Poutasse EF: Clinical evaluation of sodium nitroprusside as a hypotensive agent. Anesthesiology 1962;23:193–199.

24. Dimant S, Piper CA, Murphy TO: Pacemaker-controlled hypotension in surgery. Surgery 1967;62:663–669.

25. Fahmy NR: Nitroglycerin as a hypotensive drug during general anesthesia. Anesthesiology 1978;49:17–20.

26. Zimpfer M, Fitzal S, Tonczar L: Verapamil as a hypotensive agent during neuroleptanaesthesia. Br J Anaesth 1981;53:885–889.

27. Reves JG, Kissin I, Lell WA, Tosone S: Calcium entry blockers: uses and implications for anesthesiologists. Anesthesiology 1982;57:504–518.

28. Fukunaga AF, Facke WE, Bloor BC: Hypotensive effects of adenosine and adenosine triphosphate compared to sodium nitroprusside. Anesth Analg 1982;61:273–278.

29. Kassell NF, Boarini DJ, Olin JJ, Sprowell JA: Cerebral and systemic circulatory effects of arterial hypotension induced by adenosine. J Neurosurg 1983;58:69–76.

30. Goto F, Fujita T: Prostaglandins and circulation. Circ Control 1980;1:139–146.

31. Taneyama C, Goto H, Benson KT, Unruh GK, Arakawa K: Baroreceptor reflex response to acute blood loss during induced hypotension—a comparison of sodium nitroprusside, prostaglandin E1 and trimethaphan. Masui 1990;39:581–587.

32. Enderby GEH: Historical review of the practice of deliberate hypotension. In: Enderby GEH, ed: Hypotensive Anaesthesia. Edinburgh, Churchill Livingstone, 1985:75–91.

33. Lassen NA: Cerebral blood flow and oxygen uptake. Physiol Rev 1959;39:183–238.

34. Hoffman WE, Miletich DJ, Albrecht RF: The influence of antihypertensive therapy on cerebral autoregulation in aged hypertensive rats. Stroke 1982;13:701–704.

35. Shapiro H: Cerebral blood flow and anesthetics. In: Annual Refresher Course Lectures. American Society of Anesthesiologists, 1988;154:1.

36. Harp JR, Wollman H: Cerebral metabolic effects of hyperventilation and deliberate hypotension. Br J Anaesth 1973;45:256–262.

37. Artru AA: Partial preservation of cerebral vascular responsiveness to hypocapnia during isoflurane-induced hypotension in dogs. Anesth Analg 1986;65:660–666.

38. Artru AA: Cerebral vascular responses to hypocapnia during nitroglycerin-induced hypotension. Neurosurgery 1985;16:468–472.

39. Artru AA, Colley PS: Cerebral blood flow response to hypocapnia during hypotension. Stroke 1984;15:878–883.

40. Newman B, Gelb AW, Lam AM: The effect of isoflurane-induced hypotension on cerebral blood flow and cerebral metabolic rate for oxygen in humans. Anesthesiology 1986;64:307–310.

41. Ishikawa T, Funatsu N, Okamoto K, Takeshita H, McDowell DG: Blood-brain barrier function following drug-induced hypotension in the dog. Anesthesiology 1983;59:526–531.

42. Artru AA: Cerebral metabolism and EEG during combination of hypocapnia and isoflurane-induced hypotension in dogs. Anesthesiology 1986;65:602–608.

43. Artru AA, Wright K, Colley PS: Cerebral effects of hypocapnia plus nitroglycerin-induced hypotension in dogs. J Neurosurg 1986;64:924–931.

44. Artru AA: Cerebral metabolism and the electroencephalogram during hypocapnia plus hypotension induced by sodium nitroprusside or trimethaphan in dogs. Neurosurgery 1986;18:36–44.

45. Lermon J: Controlled hypotension. In: Gregory GA, ed: Pediatric Anesthesia, 2nd ed. New York, Churchill Livingstone, 1989.

46. Enderby GEH: Postural ischaemia and blood-pressure. Lancet 1954;1:185–187.

47. Enderby GEH: Some observations on the practice of deliberate hypotension. Br J Anaesth 1975;47:743–744.

48. Eckenhoff JE, Enderby GEH, Larson A, Edridge A, Judevine DE: Pulmonary gas exchange during deliberate hypotension. Br J Anaesth 1963;35:750–759.

49. Casthely PA, Lear S, Cottrell JE, Lear E: Intrapulmonary shunting during induced hypotension. Anesth Analg 1982;61:231–235.

50. Hales C, Slate J, Westphal D: Blockade of alveolar

hypoxic pulmonary vasoconstriction by sodium nitroprusside and nitroglycerin. Am Rev Respir Dis 1978;115:335.

51. Carlsson AJ, Bindslev L, Hedenstierna G: Hypoxia-induced pulmonary vasoconstriction in the human lung: the effect of isoflurane anesthesia. Anesthesiology 1987;66:312–316.

52. Petrozza PH: Induced hypotension. Int Anesthesiol Clin 1990;28:223–229.

53. Ganong WF: Review of Medical Physiology. Norwalk, Appleton and Lange, 1989:600.

54. Strunn L: Organ perfusion during controlled hypotension. Br J Anaesth 1975;47:793–798.

55. McDougal WS: Renal perfusion/reperfusion injuries. J Urol 1988;140:1325–1330.

56. Sood S, Jayalaxmi TS, Vijayaraghavan S, Nundy S: Use of sodium nitroprusside induced hypotensive anaesthesia for reducing blood loss in patients undergoing lienorenal shunts for portal hypertension. Br J Surg 1987;74:1036–1038.

57. Fahmy NM: Indications and contraindications for deliberate hypotension with a review of its cardiovascular effects. Int Anesthesiol Clin 1979;17:175–187.

58. Yamada S, Brauer F, Knierim D, Purtzer T, Fuse T, Hayward W, Lobo D, Dayes L: Safety limits of controlled hypotension in humans. Acta Neurochir Suppl 1988;42:14–17.

59. Little DM: Induced hypotension during anesthesia and surgery. Anesthesiology 1955;16:320–332.

60. Enderby GEH: A report on mortality and morbidity following 9,107 hypotensive anaesthetics. Br J Anaesth 1961; 33:109–113.

61. Way GL, Clarke HL: An anaesthetic technique for prostatectomy. Lancet 1959;2:888.

62. Linacre JL: Induced hypotension in gynaecological surgery. Br J Anaesth 1961;33:45–50.

63. Rollason WN, Robertson GS, Cordiner CM, Hall DJ: A comparison of mental function in relation to hypotensive and normotensive anaesthesia in the elderly. Br J Anaesth 1971;43:561–566.

64. Rollason WN, Hough JM: A study of hypotensive anaesthesia in the elderly. Br J Anaesth 1960;32:276–285.

65. Rollason WN, Hough JM: A re-examination of some electrocardiographic studies during hypotensive anaesthesia. Br J Anaesth 1969;41:985–986.

66. Grace AH: Prostatectomy under hypotensive anaesthesia. Proc R Soc Med 1961;54:1130–1132.

67. Cole PV: The safe use of sodium nitroprusside. Anaesthesia 1978;33:473–477.

68. Tough ICK: Induced hypotension and post operative bleeding. Anaesthesia 1960;15:154–157.

69. Chemello PD, Nelson SR, Wolford LM: Finger injury resulting from pulse oximeter probe during orthognathic surgery. Oral Surg Oral Med Oral Pathol 1990;69:161–163.

70. Warner WA, Shumrick DA, Caffrey JA: Clinical investigation of prolonged induced hypotension in head and neck surgery. Br J Anaesth 1970;42:39–44.

71. Persheau RA, Modell JH, Bright RN, Shirley PD: Suspected sodium nitroprusside induced cyanide intoxication. Anesth Analg 1977;56:533–536.

72. Macrae WR, Owen M: Severe metabolic acidosis following hypotension induced with sodium nitroprusside. Br J Anaesth 1974;46:795–797.

73. Merrifield AJ, Blundell MD: Toxicity of sodium nitroprusside. Br J Anaesth 1974;46:324.

74. Davies DW, Kadar D, Steward DJ, Munro IR: A sudden death associated with the use of sodium nitroprusside for induction of hypotension during anaesthesia. Can Anaesth Soc J 1975;22:547–552.

75. Jack RD: Toxicity of sodium nitroprusside. Br J Anaesth 1974;46:952.

76. Hugosson R, Hogstrom S: Factors disposing to morbidity in surgery of intracranial aneurysms with special regard to deep controlled hypotension. J Neurosurg 1973;38:561–567.

77. Prys-Roberts C, Millard RK: Self-tuning adaptive control of induced hypotension in humans: a comparison of isoflurane and sodium nitroprusside. J Clin Monit 1990;6:236–240.

78. Mackenzie AF, Colvin JR, Kenny GNC, Bisset WIK: Closed loop control of arterial hypertension following intracranial surgery using sodium nitroprusside. A comparison of intraoperative halothane or isoflurane. Anaesthesia 1993;48:202–204.

79. Wang HH, Liu LMP, Katz RL: A comparison of the cardiovascular effects of sodium nitroprusside and trimethaphan. Anesthesiology 1977;46:40–48.

80. Enderby GEH: Pharmacological blockade. Postgrad Med J 1974;50:572–575.

81. Adams AP: Techniques of vascular control for deliberate hypotension during anaesthesia. Br J Anaesth 1975;47:777–792.

82. Atkinson RS, Rushman GB, Lee JA: A Synopsis of Anaesthesia, 10th ed. Bristol, IOP Publishing Ltd., 1987:299–310.

83. Gallagher DM, Milliken RA: Induced hypotension for orthognathic surgery. J Oral Surgery 1979;37:47–51.

84. Ivankovich AD, Miletich DJ, Tinker JH: Sodium nitroprusside: metabolism and general considerations. Int Anesthesiol Clin 1978;16:1–29.

85. Magness A, Yashon D, Locke G, Wiederholt W, Hunt WE: Cerebral function during trimethaphan-induced hypotension. Neurology 1973;23:506–509.

86. Michenfelder JD, Theye RA: Canine systemic and cerebral effects of hypotension induced by hemorrhage, trimethaphan, halothane, or nitroprusside. Anesthesiology 1977; 46:188–195.

87. Brittain RT, Levy GP: A review of the animal pharmacology of labetalol, a combined α- and β-adrenoceptor-blocking drug. Br J Clin Pharmacol 1976;3:681–699.

88. Scott DB, Buckley FP, Drummond GB, Littlewoods DG, Macrae WR: Cardiovascular effects of labetalol during halothane anaesthesia. Br J Clin Pharmacol 1976;3:817–821.

89. Van Aken H, Puchstein C, Schweppe ML, Heinecke A: Effect of labetalol on intracranial pressure in dogs with and without intracranial hypertension. Acta Anaesthesiol Scand 1982;26:615–619.

90. Carswell DJ, Varkey GP, Drake CG: Labetalol for controlled hypotension in surgery for intracranial aneurysm. Can Anaesth Soc J 1981;28:505.

91. Cottrell JE, Van Aken H, Gupta B, Turndorf H: Induced hypotension. In: Cottrell JE, Turndorf H, eds: Anesthesia and Neurosurgery, 2nd ed. St Louis, CV Mosby, 1986.

92. Needleman P, Jakschik B, Johnson EM: Sulfhydryl requirement for relaxation of vascular smooth muscle. J Pharmacol Exp Ther 1973;187:324–331.

93. Kreye VAW: Sodium nitroprusside. In Scriabine, A., ed: Pharmacology of Antihypertensive drugs, New York, Raven Press, 1980:373.

94. Hauss J, Schönleben K, Bünte H, Spiegel H-U, Wendt M, Themann H: Nitroglycerin and nitroprusside induced hypotension/Different effects of hemodynamics and local oxygen supply in myocardium, liver and skeletal muscle. Arzneimittelforschung 1980;30(II):2213–2214.

95. Cole P: Sodium nitroprusside. In: Hewer CL, Atkinson RS, eds: Recent Advances in Anaesthesia and Analgesia. London, Churchill Livingstone, 1979:139–149.

96. Tinker JH, Michenfelder JD: Sodium nitroprusside: pharmacology, toxicology, and therapeutics. Anesthesiology 1976;45:340–351.

97. Cottrell JE, Casthely PA, Brodie JD, Patel K, Klein A, Turndorf H: Prevention of nitroprusside-induced cyanide toxicity with hydroxocobalamin. N Engl J Med 1978;298:809–811.

98. Khambatta NJ, Stone JA, Khan LW: Hypertension following sodium nitroprusside. Physiologist 1978;21:64.

99. Thomsen LJ, Riisager S, Jensen KA, Bünemann L: Cerebral blood flow and metabolism during hypotension induced with sodium nitroprusside and captopril. Can J Anaesth 1989; 36:392–396.

100. Stead SW, Bloor BC: The effects of captopril on the renin-angiotensin system and the sympathetic nervous system during sodium nitroprusside-induced hypotension in the halothane-anesthetized rabbit. J Cardiovasc Pharmacol 1990;15: 465–471.

101. Stead SW, Bloor BC: Enalaprilat effects renin-angiotensin and adrenergic response to induced hypotension in the rabbit. J Cardiovasc Pharmacol 1990;16:154–162.

102. Mehta P, Mehta J, Miale TD: Nitroprusside lowers platelet count. N Engl J Med 1978;299:1134.

103. Pffeiderer T: Sodium nitroprusside, a very potent platelet disaggregating substance. Acta Univ Carol 1972;53:247.

104. Miller R, Toth C, Silva DA, Hollis PH, Thys DM, Tausk HC: Nitroprusside versus a nitroprusside-trimethaphan mixture: a comparison of dosage requirements and hemodynamic effects during induced hypotension for neurosurgery. Mt Sinai J Med 1987;54:308–312.

105. Dinmore P: Combined use of trimethaphan and sodium nitroprusside. Br J Anaesth 1977;49:1070.

106. Macrae WR, Wildsmith JAW, Dale BAB: Induced hypotension with a mixture of sodium nitroprusside and trimethaphan camsylate. Anaesthesia 1981;36:312–315.

107. Wildsmith JAW, Sinclair CJ, Thorn J, Macrae WR, Fagan D, Scott DB: Hemodynamic effects of induced hypotension with a nitroprusside-trimethaphan mixture. Br J Anaesth 1983;55:381–389.

108. Fahmy NR: Nitroprusside versus nitroprusside-trimethaphan mixture for induced hypotension. Hemodynamic

effects and cyanide release. Clin Pharmacol Ther 1985;37: 264–270.

109. Nakazawa K, Taneyama C, Benson KT, Unruh GK, Goto H: Mixtures of sodium nitroprusside and trimethaphan for induction of hypotension. Anesth Analg 1991;73:59–63.

110. Shah N, Del Valle O, Edmondson R, Acampora G, Dwyer D, Matarazzo D, Rogatko A, Thorne A, Bedford RF: Esmolol infusion during nitroprusside-induced hypotension: impact on hemodynamics, ventricular performance, and venous admixture. J Cardiothorac Vasc Anesth 1992;6:196–200.

111. Edmondson R, Del Valle O, Shah N, Wong G, Dwyer D, Matarazzo D, Thorne A, Coffey C, Bedford R: Esmolol for potentiation of nitroprusside-induced hypotension: impact on the cardiovascular, adrenergic, and renin-angiotensin systems in man. Anesth Analg 1989;69:202–206.

112. Anderson JA: Deliberate hypotensive anesthesia for orthognathic surgery: controlled pharmacologic manipulation of cardiovascular physiology. Int J Adult Orthodon Orthognath Surg 1986;1:133–159.

113. Flaherty JT, Reid PR, Kelly DT, Taylor DR, Weisfeldt ML, Pitt B: Intravenous nitroglycerin in acute myocardial infarction. Circulation 1975;51:132–139.

114. Cossum PA, Roberts MS, Galbraith AJ, Boyd GW: Loss of nitroglycerin from intravenous infusion sets. Lancet 1978;2:345–350.

115. Needleman P: Organic nitrate metabolism. Ann Rev Pharmacol Toxicol 1976;16:81–93.

116. Hill AB, De Rosayro AM, Nahrwold MD, Tait AR: Vascular uptake of nitroglycerin. Anesthesiology 1980;53:S82.

117. Ablad B: A study of the mechanism of the hemodynamic effects of hydralazine in man. Acta Pharmacol Toxicol 1963;20:1.

118. Bourreli B, Pinaud M, Passuti N, Gunst JP, Drouet JC, Remi JP: Additive effects of dihydralazine during enflurane or isoflurane hypotensive anaesthesia for spinal fusion. Can J Anaesth 1988;35:242–248.

119. Shapira Y, Gertel M: New drugs for deliberate hypotension in anesthesia. Harefuah 1988;114:69–72.

120. Flamm ES, Adams HP Jr, Beck DW, Pinto RS, Marler JR, Walker MD, Godersky JC, Loftus CM, Biller J, Boarini DJ, O'Dell C, Banwart RN, Kongable G: Dose-escalation study of intravenous nicardipine in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg 1988;68:393–400.

121. Kaplan JA: The role of nicardipine during anesthesia and surgery. Clin Ther 1989;11:84–93.

122. Begon C, Dartayet B, Edouard A, David D, Samii K: Intravenous nicardipine for treatment of intraoperative hypertension during abdominal surgery. J Cardiothorac Anesth 1989; 3:707–711.

123. Kawaguchi M, Furuya H, Kurehara K, Yamada M: Effects of nicardipine on cerebral vascular responses to hypocapnia and blood flow velocity in the middle cerebral artery. Stroke 1991;22:1170–1172.

124. Bernard JM, Pinaud M, Francois T, Babin M, Macquin-Mavier I, Letenneur J: Deliberate hypotension with nicardipine or nitroprusside during total hip arthroplasty. Anesth Analg 1991;73:341–345.

125. Ikeda K, Minami Y, Yoshimatsu N, Fujita R, Ikeda T,

Isshiki A: A comparison of induced hypotensive anesthesia using trimethaphan, prostaglandin E1 and nicardipine for neurosurgery. Masui 1991;40:400–405.

126. Mazzoni P, Griffin JP, Cottrell JE, Hartung J, Capuano C, Epstein JM: Intracranial pressure during diltiazem-induced hypotension in anesthetized dogs. Anesth Analg 1985;64:1001–1004.

127. Van Aken H, Puchstein C, Fitch W, Graham DI: Haemodynamic and cerebral effects of ATP-induced hypotension. Br J Anaesth 1984;56:1409–1415.

128. Sollevi A, Lagerkranser M, Irestedt L, Gordon E, Lindquist C: Controlled hypotension with adenosine in cerebral aneurysm surgery. Anesthesiology 1984;61:400–405.

129. Kien ND, White DA, Reitan JA, Eisele JH Jr: Cardiovascular function during controlled hypotension induced by adenosine triphosphate or sodium nitroprusside in the anesthetized dog. Anesth Analg 1987;66:103–110.

130. Öwall A, Järnberg PO, Brodin LA, Sollevi A: Effects of adenosine-induced hypotension on myocardial hemodynamics and metabolism in fentanyl anesthetized patients with peripheral vascular disease. Anesthesiology 1988;68:416–421.

131. Öwall A, Lagerkranser M, Sollevi A: Effects of adenosine-induced hypotension on myocardial hemodynamics and metabolism during cerebral aneurysm surgery. Anesth Analg 1988;67:228–232.

132. Lagerkranser M, Bergstrand G, Gordon E, Irestedt L, Lindquist C, Stånge K, Sollevi A: Cerebral blood flow and metabolism during adenosine-induced hypotension in patients undergoing cerebral aneurysm surgery. Acta Anaesthesiol Scand 1989;33:15–20.

133. Waaben J, Husum B, Hansen AJ, Gjedde A: Regional cerebral blood flow and glucose utilization during hypocapnia and adenosine-induced hypotension in the rat. Anesthesiology 1989;70:299–304.

134. Zall S, Eden E, Winso I, Volkmann R, Sollevi A, Ricksten SE: Controlled hypotension with adenosine or sodium nitroprusside during cerebral aneurysm surgery: effects on renal hemodynamics, excretory function, and renin release. Anesth Analg 1990;71:631–636.

135. Sollevi DB, Lagerkranser M, Andrews M, Irestedt L: Relationship between arterial and venous adenosine levels and vasodilatation during ATP- and adenosine-infusion in dogs. Acta Physiol Scand 1984;120:171–176.

136. Gross GJ, Woltier DC, Hardman HF: Effect of adenosine on myocardial oxygen balance. J Pharmacol Exp Ther 1976;196:445–454.

137. James TN: The chronotropic action of ATP and related compounds studied by direct perfusion of the sinus node. J Pharmacol Exp Ther 1965;149:233–247.

138. Hedqvist P, Fredholm BB: Inhibitory effects of adenosine on adrenergic neuroeffector transmission in the rabbit heart. Acta Physiol Scand 1979;105:120–122.

139. Fukunaga AF, Ikeda K, Matsuda L: ATP-induced hypotensive anesthesia during surgery. Anesthesiology 1982;57:A65.

140. Lokhandwola MF: Inhibition of cardiac sympathetic neurotransmission by adenosine. Eur J Pharmacol 1979;60:353–357.

141. Brunstock G: Purinergic nerves. Pharmacol Rev 1972;24:509–581.

142. Puchstein C, Van Aken H, Anger C, Thys J, Lawin P: Influence of ATP induced hypotension on intracranial pressure and intracranial compliance. Anesthesiology 1983;59:A356.

143. Dedrick DF, Mans AM, Campbell PA, Hawkins RA, Biebuyck JF: Does ATP-induced hypotension cause potentially serious metabolic complications? Anesthesiology 1982;57:A66.

144. Lagerkranser M, Andreen M, Irestedt L, Sollevi A: Controlled hypotension with the combination of dipyridamole and adenosine. Anaesthesia 1982;37(suppl):303.

145. Ahlering TE, Henderson JB, Skinner DG: Controlled hypotensive anesthesia to reduce blood loss in radical cystectomy for bladder cancer. J Urol 1983;129:953–954.

146. Hirota K, Muraoka M, Takahashi S, Ogasawara E, Ishihara H, Matsuki A: Effect of induced hypotension with prostaglandin E1 or trimethaphan on endocrine functions in surgical patients. Masui 1991;40:763–768.

147. Hoka S, Yoshitake J, Dan K, Goto Y, Honda N, Morioka T, Muteki T, Okuda Y, Shigematsu A, Takasaki M, Totoki T, Yoshimura N, et al: Intra-operative blood pressure control by prostaglandin E_1 in patients with hypertension and ischemic heart disease. A multi-center study. J Anesth 1993;7:173–183.

148. Carlson LA, Ekelund LG, Oro L: Circulatory and respiratory effects of different doses of prostaglandin E1 in man. Acta Physiol Scand 1969;75:161–169.

149. Nakano J, McCurdy JR: Cardiovascular effects of prostaglandin E1. J Pharmacol Exp Ther 1967;156:538–547.

150. Brunsting IA, Salter DR, Murphy CE, Abd-Elfattah AS, Goldstein JP: The importance of load-independent analysis in assessment of the inotropic effect of prostaglandin E1 in vivo. J Thorac Cardiovasc Surg 1988;95:432–442.

151. Goto F, Otani E, Kato S, Fujita T: Prostaglandin E1 as a hypotensive drug during general anaesthesia. Anaesthesia 1982;37:530–535.

152. Zijlstra WG, Brunsting JR, Ten Hoor F, Vergroesen AJ: Prostaglandin E1 and cardiac arrhythmia. Eur J Pharmacol 1972;18:392–395.

153. Kelliher GJ, Glenn TM: Effect of prostaglandin E1 on ouabain-backed arrhythmias. Eur J Pharmacol 1973;24:410–414.

154. Kitaguchi K, Nakajima T, Takaki O, Uchida O, Hayashi Y, Ohnishi Y, Shibata H, Kuro M: The change in cerebral blood flow during hypotensive anesthesia induced by prostaglandin E1. Masui 1992;41:766–771.

155. Diaz JH, Lockhart CH: Hypotensive anaesthesia for craniectomy in infancy. Br J Anaesth 1979;51:233–235.

156. Saarnivaara L, Brander P: Comparison of three hypotensive anaesthetic methods for middle ear microsurgery. Acta Anaesthesiol Scand 1984;28:435–442.

157. Thompson GE, Miller RD, Stevens WC, Murray WR: Hypotensive anesthesia for total hip arthroplasty: a study of blood loss and organ function (brain, heart, liver, and kidney). Anesthesiology 1978:48:91–96.

158. McNeill TW, DeWald RL, Kuo KN, Bennett EJ, Salem MR: Controlled hypotensive anesthesia in scoliosis surgery. J Bone Joint Surg 1974;56:1167–1172.

159. Madsen JB, Cold GE, Hansen ES, Bardrum B, Kruse-

Larsen C: Cerebral blood flow and metabolism during isoflu-rane-induced hypotension in patients subjected to surgery for cerebral aneurysms. Br J Anaesth 1987;59:1204–1207.

160. Macnab MSP, Manninen PH, Lam AM, Gelb AW: The stress response to induced hypotension for cerebral aneurysm surgery: a comparison of two hypotensive techniques. Can J Anaesth 1988;35:111–115.

161. Woodcock TE, Millard RK, Dixon J, Prys-Robers C: Clonidine premedication for isoflurane-induced hypotension. Br J Anaesth 1988;60:388–394.

162. Warltier DC, Pagel PS: Cardiovascular and respiratory actions of desflurane: Is desflurane different from isoflurane. Anesth Analg 1992;75:S17–S31.

163. Young WL: Effects of desflurane on the central nervous system. Anesth Analg 1992;75:S32–S37.

164. Jordan WS, Graves CL, Boyd WA, Ueda I, Roberts TS: Cardiovascular effects of three technics for inducing hypoten-sion during anesthesia. Anesth Analg 1971;50:1059–1068.

165. Savege TM: New anaesthetic drugs and techniques—enflurane, etomidate and total intravenous anaesthesia. Rec Adv Anaesth Analg 1979;13:1–22.

166. Bergman S, Hoffman WE, Gans BJ, Miletich DJ, Al-brecht RF: Blood flow to oral tissues: an experimental study with enflurane, sodium nitroprusside, and nitroglycerin. J Oral Maxillofac Surg 1982;40:13–17.

167. Ornstein E, Matteo RS, Weinstein JA, Schwartz AE: A randomized controlled trial of esmolol for deliberate hypoten-sion. Anesthesiology 1987;67:A423.

168. Rodrigo C: Disorders of cardiac rhythm during anes-thesia and sedation for oral and maxillofacial surgery. Oral Max-illofac Surg Clin North Am 1992;4:781–794.

169. Hellewell J, Potts MW: Propranolol during controlled hypotension. Br J Anaesth 1966;38:794–801.

170. Hewitt PB, Lord PW, Thornton HL: Propranolol in hy-potensive anaesthesia. Anaesthesia 1967;22:82–90.

171. Simpson DA, Ireland J: Hypotensive and normotensive anaesthesia in total hip replacement—a comparative study. Br J Clin Pract 1983;37:16–18.

172. Eichwede F, Komar K, Miller R, Grote B, Tarnow J: Preoperative treatment with β blockers and isoflurane anesthe-sia. Hemodynamic interactions in patients with coronary dis-ease. Anaesthetist 1990;39:361–366.

173. Angaran DM, Schultz NJ, Tschida VH: Esmolol hydro-chloride: an ultrashort-acting, β-adrenergic blocking agent. Clin Pharm 1986;5:288–303.

174. Gray RJ, Bateman TM, Czer LSC, Conklin C, Matloff JM: Use of esmolol in hypertension after cardiac surgery. Am J Cardiol 1985;56:49F–56F.

175. Hilgenberg JC: Comparison of the pharmacology of vecuronium and atracurium with that of other currently avail-able muscle relaxants. Anesth Analg 1983;62:524–531.

176. Katz RL: Clinical neuromuscular pharmacology of pan-curonium. Anesthesiology 1971;34:550–556.

177. Bahlman SH, Eger EI II, Halsey MJ, Stevens WC, Shakespeare TF, Smith NT, Cromwell TH, Fourcade H: The cardiovascular effects of halothane in man during spontaneous ventilation. Anesthesiology 1972;36:494–502.

178. Hunter AR: Neurosurgical Anaesthesia. Oxford, Black-well Scientific Publications, 1964:147.

179. Bernard JM, Quintin L, Pinaud M: Clonidine: from the treatment of hypertension to its use in anesthesia. II: perioper-ative use. Ann Fr Anesth Reanim 1990;9:423–432.

180. Fridrich KL: Anesthetic techniques to reduce blood loss and transfusion therapy. Oral Maxillofac Surg Clin North Am 1992;4:863–864.